

May 20th, 12:30 PM

Bioavailability of the Antimalarial Drug Artemisinin Delivered Orally as Dried Leaves of *Artemisia annua*: the Role of Solubility and Protein.

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Matthew Desrosiers and Pamela Weathers, "Bioavailability of the Antimalarial Drug Artemisinin Delivered Orally as Dried Leaves of *Artemisia annua*: the Role of Solubility and Protein." (May 20, 2016). *UMass Center for Clinical and Translational Science Research Retreat*. Paper 8.
http://escholarship.umassmed.edu/cts_retreat/2016/posters/8

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Bioavailability of the Antimalarial Drug Artemisinin Delivered Orally as Dried Leaves of *Artemisia annua*: the Role of Solubility and Protein.

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Malaria treatment using orally consumed dried leaves of the artemisinin producing GRAS plant *Artemisia annua* has recently shown promise. Previously we showed, oral consumption of *A. annua* dried leaves (DLA) yielded >40 times more artemisinin in the blood of mice than treatment with pure artemisinin. Using the Caco-2 cell culture model of the human intestinal epithelium, we also showed that compared to pure artemisinin, digested DLA doubled the permeability (P_{app}). Here, using simulated human digestion, we show that artemisinin solubility is about seven times higher in digestates of DLA than in digestates of pure artemisinin, likely contributing to its enhanced bioavailability. Digestion with pure artemisinin combined with levels of essential oils comparable to that in DLA increased the solubility of artemisinin 2.5 times indicating essential oils play a role in increasing artemisinin solubility. Interestingly, increasing the starting concentration of artemisinin in Caco-2 transport studies did not alter P_{app} . Considering malaria affects mostly young children and about 60% of the population experiences DLA as unpleasant tasting, we also tested several protein rich foods as potential flavor-masking agents for their effects on bioavailability. We showed that while taste was masked, peanuts and a peanut-based paste used to treat malnutrition, PlumpyNut, reduced artemisinin and flavonoid levels in simulated digestates, respectively, likely decreasing their bioavailability. Experiments to further investigate the role of several compounds such as camphor, a principle component of the essential oil fraction, and flavonoids on artemisinin solubility and bioavailability are ongoing. The results of these experiments are helping to explain the increased bioavailability afforded by DLA seen in mice.

Acknowledgements

We thank Capsugel for providing capsules, Dr. Melissa Towler of Worcester Polytechnic Institute for advice in artemisinin and flavonoid analysis, Dr. Jill Rulfs and Abbie White of Worcester Polytechnic Institute for the taste tasting survey, and Worcester Polytechnic Institute for partially supporting Mr. Desrosiers. We are also grateful for Award Number NIH-R15AT008277-01 from the National Center for Complementary and Integrative Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Complementary and Integrative Health or the National Institutes of Health.

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